REMARKS

The claims pending and under examination in this case are 1-22. Applicants have replaced these claims by new claims 23-40 and have cancelled claims 1-22. The new claims are believed to define patentable subject matter over the art of record in this case. As the Examiner has inquired regarding the terms "incorporated" and "encapsulated", Applicants wish to clarify their meaning in this application. As liposomes, due to their structure, possess the ability to trap water soluble molecules in the internal aqueous compartments and to trap water insoluble molecules in the lipid bi-layer, the term "encapsulation" is used for the first case and "incorporation" for the second one. Sometime the term "incorporation" can have a more general definition and can be used for both cases. In the claims, to be most precise, it is preferred to use the term "incorporated" where appropriate.

Regarding the question of mixing populations of particles, some bigger and lower in diameter than 100 nm, the following is submitted in explanation. It is known from the literature that, upon parenteric administration, large liposomes will be accumulated in liver and spleen and only small liposomes can circulate longer and achieve other sites in the organism. The definition of the particle diameter associated with each of the terms "large" and "small" is difficult or impossible. Because of the large numbers of particles in any given population, a Gaussian type distribution prevails. By selecting different groups of

populations of particles, different target organs can be reached as, for example, the liver, the spleen and the bone marrow and skin where so-called large liposomes reach the liver and spleen and the small liposomes reach the bone marrow and skin. It has been found that the value of the 100 nm particle is the most common value for the theoretical separation between populations that are captured in liver and spleen and the population able to circulate longer and reach other sites such as the bone marrow and skin.

In summary, it can be said that mixing populations of different particle size, namely bigger and lower than 100 nm, is a key feature for the pharmaceutical use of the liposome particles according to this invention and has not as yet been known, nor is it obvious. The incorporation of these features in the new first claim 23 defines a new product with new characteristics for a new utilization.

The principal citation of the Examiner WO 95/31970 which is relied upon by the Examiner to reject the formulation claims as lacking novelty or anticipated by the reference, relates to a method for the production of liposomal microencapsulated product for agricultural formulations. Neither the method, nor the purpose, nor the achieved liposomal stock solutions have anything that can be related to the presently claimed invention. The formulation obtained by the process of the reference is totally different from that of the present application. The reference

process cannot be used in the treatment of leishmaniasis for several reasons: impurities, obtained diameters, presence of organic solvents. The relevance of this document is questioned. The only similarity is that it contains one of the possible lipids and states that the pesticide could be trifluralin, but everything else is very different. The liposomes prepared according to the present application which contain trifluralin are so different and are incorporated into the vesicle with populations of particles specifically designed to reach the diverse intended organs.

Turning now to the references relied upon for the rejection of the claims to the formulations as obvious, the Steck literature concerns liposomal formulations of antimonals as Rao. However, none of these refers to trifluralin and none of their preparation methods bear any similarity to those of the present application. As for the UK patent application, it is important to note that the use of dehydration is not obvious in the present case. Trifluoralin will be removed from liposomes during dehydration. Therefore, it is necessary to ensure that it does not happen and the presently claimed process does address that need.

Reconsideration of the rejection of the claims to the liposome formulation and the method of preparing the formulation and using it is respectfully solicited in view of the foregoing arguments and amendments.

It is believed that the claims now define patentable subject matter and favorable action and allowance of the present

application is respectfully solicited.

Should the Examiner wish to contact Applicants' representative, he may do so by telephoning Edward H. Valance, Reg. No. 19,896, at (703) 205-8000 in the Washington Metropolitan area.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of two (2) months to January 15, 2002 in which to file a reply to the Office Action. The required fee of $400.00 is enclosed herewith.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By: Edward H. Valance #19896
FOR Joseph A. Kolasch
Reg. No. 22,463

P. O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

JAK/EHV/bsh

Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKING TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 1-22 have been cancelled.

Claims 23-40 have been added